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Intravenous Busulfan and Melphalan, Tacrolimus, and Short-Course Methotrexate Followed by Unmodified HLA-Matched Related or Unrelated Hematopoietic Stem Cell Transplantation for the Treatment of Advanced Hematologic Malignancies

Trudy N. Small,[1] James W. Young,[2] Hugo Castro-Malaspina,[2] Susan Prockop,[1] Andrew Wilton,[3] Glenn Heller,[3] Farid Boulad,[1] Michelle Chiu,[1] Katherine Hsu,[2] Ann Jakubowski,[2] Nancy A. Kernan,[1] Miguel-Angel Perales,[2] Richard J. O'Reilly,[1] Esperanza B. Papadopoulos[2]

[1]Department of Pediatrics, Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York, New York, [2]Department of Medicine, Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York, New York, [3]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York

Correspondence and reprint requests: Trudy N. Small, MD, Department of Pediatrics, Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021 (e-mail: smallt@mskcc.org).

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ABSTRACT

Results of allogeneic hematopoietic stem cell transplantation (HCT) to treat advanced leukemia or myelodysplastic syndrome (MDS) remain poor due to excessive relapse and transplant-related mortality. To improve transplant outcome in this patient population, 43 patients (median age, 46.1 years) with high-risk or advanced lymphoid (n = 5) or myeloid malignancy (n = 38) were prospectively enrolled on a pilot trial of cytoreduction with intravenous busulfan and melphalan followed by an unmodified HLA-A, -B, and –DRβ1–matched related (n = 18) or unrelated (n = 25) HCT. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and methotrexate. Thirty-four patients had ≥ 5% blasts at the time of HCT; 12 of these had > 20% blasts. Seventeen patients had unfavorable cytogenetics, 8 patients underwent transplantation for secondary MDS or acute myelogenous leukemia, and 4 patients had relapsed after a previous allogeneic transplantation. Although mucositis was the most significant regimen-related toxicity, requiring the addition of folinic acid rescue and failure to receive all 4 doses of methotrexate in 23 patients, the nonrelapse mortality at 30 and 100 days was low at 0% and 16%, respectively. The cumulative incidence of grade II-IV acute GVHD was 24%, and that of extensive chronic GVHD was 7%. With a minimum follow-up of 18 months, the estimated 3-year overall survival is 37% and the estimated disease-free survival (DFS) is 33%. For 18 patients with MDS (≤ RAEB-2) or high-risk myeloproliferative disorder, the estimated 3 year DFS is 61%. These data demonstrate the curative potential of this regimen in patients with high-risk myeloid malignancies.

KEY WORDS

Transplantation • Leukemia • MDS

INTRODUCTION

Currently more than 60% of patients undergoing transplantation for acute leukemia in first or second remission, de novo myelodysplastic syndrome (MDS) with < 5% blasts, or chronic myelogenous leukemia (CML) in the early first chronic phase can achieve long-term disease-free survival (DFS) after matched related [1-7] or unrelated [6-10] hematopoietic stem cell transplantation (HCT). Unfortunately, the outcome of patients with more advanced disease remains poor. For patients with primary induction failure, late remission (at or beyond third continuous remission [CR3]),

refractory relapse, or advanced MDS, event-free survival rates of 7%-36% have been reported after cytoreduction with total body irradiation (TBI) and cyclophosphamide (Cy), TBI and etoposide (VP), and busulfan (BU) and Cy [11-18]. Addition of a third agent to the conditioning regimen to makes such combinations as TBI/Cy/VP [19], thiotepa/Bu/Cy [20], Bu/Cy/VP [21], and anti-CD45/TBI/Cy [22], has not improved DFS in patients with advanced disease.

In 1996, Vey et al. [23] reported the outcome of 25 adult recipients of unmodified HLA-matched related bone marrow transplantation (BMT) who underwent cytoreduction with 16 doses of oral busulfan (1 mg/kg/dose) followed by intravenous melphalan (140 mg/m^2/day). Of these 25 patients, 16 had poor-risk disease (refractory or relapsed leukemia, blastic CML, or primary refractory lymphoma). The 4-year probability for DFS was 31%. Long-term disease-free survivors included 2 patients with advanced acute leukemia and 2 patients with blastic CML. Matsuyama et al. [24] reported a 90% 5-year DFS in 30 children (acute myelogenous leukemia [AML], CR1 [n = 18] or CR2 [n = 2]; acute lymphocytic leukemia [ALL], CR1 [n = 7] or CR2 [n = 1]; or CML [n = 2]] after HLA-matched related BMT with cytoreduction with 4 days of oral busulfan (4 mg/kg/day) and 3 days of IV melphalan (60 to 70 mg/m2/day). Graft-versus-host disease (GVHD) prophylaxis consisted of methotrexate alone.

In the current trial, we evaluated the use of intravenous busulfan combined with melphalan, followed by unmodified HLA-A, -B, and -DRβ1 unrelated or HLA-matched sibling HCT in patients with high-risk hematologic malignancies. Intravenous rather than oral busulfan was used due to its more consistent and reproducible bioavailability with lower-than-expected toxicity when evaluated in heavily pretreated patients [25,26]. GVHD prophylaxis consisting of tacrolimus and short-course methotrexate was used due to this regimen's association with lower incidence and severity of acute GVHD and decreased incidence of extensive chronic GVHD [27,28]. This article describes the outcome of 43 consecutive recipients with high-risk or advanced lymphoid or myeloid malignancies enrolled on this protocol.

METHODS

Forty-four patients or their guardians signed informed consent before initiation of cytoreduction in this Institutional Review Board–approved clinical research protocol. Eligibility criteria required a diagnosis of acute leukemia at ≥ CR3; infant mixed lineage leukemia; advanced MDS (RAEB-1 or RAEB-2) as defined by the World Health Organization classification system [29]; secondary MDS or AML; juvenile myelomonocytic leukemia (JMML) as defined by the International JMML Working Group [30]; or CML beyond the second chronic phase, (accelerated or blastic phase). An HLA-A, -B, and -DRβ1–matched related or unrelated donor was required. HLA matching was established by DNA sequence-specific oligonucleotide typing for HLA-A, -B, and -DR loci. A C-locus mismatch was present in 3 unrelated HCT recipients. One patient enrolled on protocol developed pneumonia after registration but before starting chemotherapy; this patient was deemed ineligible due to the exclusion criteria of active infection. The remaining 43 patients who underwent transplantation between January 31, 2001 and April 20, 2005 compose our study group.

Patient Characteristics

The demographics and clinical characteristics of the 43 patients (18 females, 25 males) are given in Tables 1 and 2. The median patient age was 46.1 years (range, 0.6-62.0 years). Eight patients (19%) were children (under age 19 years at the time of transplantation). Eighteen patients, 7 of whom received an unrelated HCT, were over age 50 at the time of transplantation.

All patients had a high-risk or advanced hematologic malignancy (Table 2). Eight patients had secondary AML or MDS, associated with previous treatment for breast cancer (n = 2), ALL (n = 2), Ewing's sarcoma (n = 1), Hodgkin's disease (n = 1), aplastic anemia (n = 1), or MDS (n = 1). Three patients underwent transplantation while in CR3, including 2 children who had relapsed 6 months after an allogeneic BMT for ALL CR2 and 1 adult with AML, who achieved CR3 after 2 courses of gemtuzumab ozogamicin (Mylotarg). The remaining 22 patients with acute leukemia underwent transplantation with active disease, including untreated AML evolving from previous MDS (n = 1), primary induction failure (n = 4), refractory relapse (n = 13), or untreated second relapse (n = 4). Of the patients who underwent transplantation for MDS, 2 were in refractory anemia (RA), 4 were in RAEB-1, and 5 were in RAEB-2 at the time of transplantation. One patient with secondary MDS associated with an 11q23 abnormality developed RA after treatment for Ewing's sarcoma that progressed to AML. This patient underwent transplantation while in morphologic and cytogenetic remission after treatment with high-dose cytarabine and L-asparaginase.

At the time of transplantation, 34 patients had ≥ 5% bone marrow blasts. The median blast count of these 34 patients was 16% (range, 5%-81%). Cytogenetic analyses were evaluable in all 43 patients (Table 2) and were abnormal in 53% of them. Seventeen patients had unfavorable cytogenetics [31], defined as abnormalities of

Table 1. *Patient and Donor Characteristics*

	All Patients (n = 43)	Related Donor (n = 18)	Unrelated Donor (n = 25)
Age (years), median (range)	46.0 (0.6-62.0)	50.5 (7.0-62.0)	37.0 (0.6-61.0)
Sex	18 F/25 M	8 F/10 M	10 F/15 M
ALL	5	3	2
CR3	2, prior allo-BMT (n = 2)	2	0
Refractory first relapse	2	1	1
Refractory second relapse	1	0	1
AML	20	12	8
CR3	1	0	1
Untreated AML, post-MDS	1	1	0
Primary Induction failure	4	1	3
Refractory first relapse	7	6	1
Untreated second relapse	4	2	2
Refractory second relapse	3	2	1
MDS/myeloproliferative disorder (MPD)	18	4	11
Secondary MDS, RA, AML, CR1	1	0	1
RA/RA (prior RAEB-2)	1/1	0	0
RAEB-1	4	2	2
RAEB-2	5	2	3
JMML	3	0	3
CML (acc/blast crisis, acc)	1/1	0	2
Ph-myeloproliferative disorder	1	0	1
Prior allogeneic HCT	4	3	1
Treatment-related	7	1	6
Stem cell source			
Bone marrow	27	13	14
Peripheral blood	16	5	11
Patient/donor CMV serology			
Negative/negative	19	8	11
Negative/positive	5	3	2
Positive/negative	7	1	6
Positive/positive	12	7	5

chromosome 5, 7, 11q23, or trisomy 8 and/or ≥3 chromosomal abnormalities (Table 2).

Preparative Regimen

Patients received intravenous busulfan (Busulfex; Orphan Medical Co), a total of 16 doses infused every 6 hours for 4 days, followed by intravenous melphalan (45 mg/m^2/day) for 3 days. The initial busulfan dosage was based on patient age. Patients age 4 and younger received 1 mg/kg/dose; those over 4 years, 0.8 mg/kg/dose. Based on pharmacokinetic studies, the protocol was subsequently amended to adjust the initial dose to 1.1 mg/kg/dose in patients weighing < 12 kg and 0.8 mg/kg/dose for those weighing > 12 kg. First-dose pharmacokinetics were performed at the Fred Hutchinson Cancer Research Center using high-performance liquid chromatography–mass spectrometry. The busulfan dose was adjusted to reach a steady-state level of 600-900 ng/mL, with the desired level closer to 900 ng/mL. One patient who received the 16-dose course of busulfan was found to have an elevated busulfan level (1080 ng/mL) after completing therapy, and thus was given only 80% of the total melphalan dose. Due to an early graft failure in the trial after an unrelated donor HCT, equine antithymocyte globulin (ATG) (15 mg/kg/day, days −4 and −3) was added to the preparative regimen in those patients receiving unrelated donor transplants.

Table 2. *Causes of Death*

	Related	Unrelated	Total
Relapse	8	6	14
Toxicity	1 (IP)	3 (VOD, IP, TRALI)	4
GVHD	2	3	5
Infection	1 (CMV IP)	1 (sepsis)	2
Graft failure	0	1	1

IP indicates interstitial pneumonia; TRALI, transfusion-related acute lung injury [35].

GVHD Prophylaxis and Evaluation

GVHD prophylaxis consisted of 4 doses of intravenous methotrexate (15 mg/m^2 on day +1, 10 mg/m^2 on days +3, +6, and +11) and continuous-infusion intravenous tacrolimus (0.03 mg/kg/24 hours) starting on day −1. This protocol was amended after the first 20 patients were accrued to include folinic acid rescue every 6 hours for 4-6 doses, starting 24 hours after each methotrexate dose. Folinic acid was discontinued 24 hours before the subsequent methotrexate dose.

Acute GVHD was defined as any GVHD occurring < 100 days posttransplantation and was graded according to the Glucksberg criteria [32]. Chronic GVHD (ie, GVHD occurring > 100 days post-HCT) was graded as limited or extensive according to the criteria of Sullivan et al. [33].

Engraftment, Graft Failure, and Donor Chimerism

Engraftment was defined as the first of 3 consecutive days of an absolute neutrophil count (ANC) of ≥ 500 cells/μL. Primary graft failure was defined as failure to achieve an ANC of ≥ 500 cells/μL by day 28 after HCT. Platelet engraftment was defined as an untransfused platelet count of ≥ 50,000/μL for at least 3 consecutive days. Bone marrow aspirates were obtained at regular intervals posttransplantation to assess remission chimeric status. Bone marrow donor–host chimerism was assessed by polymerase chain reaction analysis of short tandem repeats using primers D5S818, D13S317, D7S820, and D16S539.

Supportive Care

All patients underwent transplantation in reverse isolation in a single room with filtered air. Seizure prophylaxis with phenytoin was administered before the first busulfan dose and continued for 24 hours after the last busulfan dose. Herpes simplex virus, fungal, and *Pneumocystis carinii* pneumonia prophylaxis was given to all patients as described previously [2]. Cytomegalovirus (CMV)-seropositive patients or those with a CMV-seropositive donor were followed for CMV antigenemia and received treatment with ganciclovir or foscarnet for positive antigenemia (> 1 cell positive/slide). Neutropenic patients with persistent fever despite 72 hours of broad-spectrum antibiotics received empiric antifungal therapy. All recipients of an unrelated transplant and those recipients of an HLA-matched related HCT whose serum IgG level was < 500 ng/dL received monthly intravenous gamma globulin (400 mg/kg/dose) for at least 3 months posttransplantation.

Biostatistics

Analyses were performed as of September 1, 2006. The Kaplan-Meier estimate was used to compute the overall survival (OS) and DFS probabilities. The cumulative incidence function was used to estimate the probability of the time to relapse, nonleukemic mortality, and GVHD. The equality of the OS and DFS rates between groups was assessed using the log-rank statistic. Gray's statistic was used to test the equality of the relapse, nonleukemic mortality, and GVHD rates between groups [34].

RESULTS

Busulfan Levels

Pharmacokinetic analyses were performed for 42 of the 43 patients. The median steady-state level achieved after the first dose was 770 ng/mL (range, 370-1199 ng/mL). In patients under age 19, the median initial busulfan steady-state level was 535 ng/mL (range, 370-1180) ng/mL; in those age 19 and older, it was 799 ng/mL (range, 566-1199 ng/mL). The initial busulfan level was below the target level (< 600 ng/mL) in 75% of children and 9% of adults and above the target level (> 900 ng/dL) in 12.5% of children and 30% of adults. The median initial busulfan level in patients who subsequently relapsed (790 ng/dL) did not significantly differ from that in patients who did not relapse (761 mg/mL).

Graft Characteristics

Twenty-seven patients received a BM transplant from an HLA-matched related (n = 15) or unrelated donor (n = 12), and 16 patients received a peripheral blood stem cell (PBSC) transplant from an HLA-matched related (n = 4) or unrelated donor (n = 12). The choice of PBSC or BM was based on the donor's preference. The median (range) total nucleated cell dose was 2.14 (0.4-9.1) $\times 10^8$/kg in BM recipients and 14.2 (2.24-605.0) $\times 10^8$/kg in PBSC recipients.

Engraftment

Forty-one of the 43 patients engrafted at a median of 15 days (range, 10 to 24 days). Primary graft failure, defined as failure to achieve an ANC of 500 cells/μL by day 28, occurred in 2 children with MDS who received an unrelated BMT. In the absence of ATG, 1 of 4 recipients of an unrelated HCT failed to engraft. In contrast, only 1 of the 21 patients who received equine ATG before an unrelated HCT experienced graft failure. Twenty-five of the 27 BM recipients engrafted at a median of 18 days (range, 11-24 days); all PBSC recipients engrafted, at a median of 13 days (range, 10-23 days). Among the 41 patients who engrafted, the time to ANC > 500 was more rapid in PBSC recipients than in BM recipients ($P < .001$). The median time to achieve an untransfused platelet count of 50,000 was 28 days (19.5 days after PBSCT and 32 days after BMT; $P = .13$).

Remission Induction

CR after transplantation was defined as < 5% marrow blasts, absence of circulating blasts, lack of chromosomal abnormalities, and donor cell engraftment. Three patients were not evaluable for remission induction due to graft failure (n = 2) or failure to have a day 30 bone marrow aspiration despite peripheral engraftment. The rate of CR in the 40 evaluable

patients was 100%, including all patients with active disease at the time of transplantation.

Regimen-Related Toxicity

The most significant toxicities associated with this protocol were mucositis and renal insufficiency. Forty patients developed grade III mucositis according to the BMT CTC Version 2.0 (Appendix V, BMT-Specific Events), and 2 patients developed grade IV mucositis requiring mechanical ventilation for airway protection. Due to significant mucositis, 21 patients received only 3 doses of methotrexate, and 2 patients received 2 doses. Six patients developed grade III renal toxicity (creatinine > 3-6 times the upper limit of normal). Four patients developed reversible renal failure due to nephrotoxic drugs (n = 2), septic shock (n = 1), or severe hemolysis (n = 1). Two patients developed veno-occlusive disease (VOD) (4.7%); these were 2 of the 5 patients in this study who had received gemtuzumab ozogamicin before transplantation.

Acute GVHD

A total of 41 patients were evaluable for the development of acute GVHD. Ten patients developed acute grade II-IV GVHD (3 grade II, 5 grade III, and 2 grade IV). The 100-day cumulative incidence of acute grade II-IV GVHD was 0.24. There was no significant difference in the incidence of grade II-IV acute GVHD between recipients of HLA-matched sibling transplants (4/18; 22%) and unrelated transplants (6/23; 26%).

Chronic GVHD

Twenty-nine engrafted patients survived more than 100 days after related (n = 14) or unrelated (n = 15) HCT and were evaluable for chronic GVHD. Limited chronic GVHD occurred in 9 patients, and extensive chronic GVHD developed in 2 patients. One patient developed an isolated but fatal acute hepatic variant of GVHD 9 months after an HLA-matched related PBSC transplant (PBSCT). Chronic GVHD occurred in 7 of 14 recipients of an HLA-matched related HCT and in 4 of 15 recipients of an unrelated HCT (P = .57).

Relapse

To date, 17 patients have relapsed (Figure 1). Relapse occurred at a median of 9.8 months (range, 2.6-29.5 months) posttransplantation. The cumulative incidence of relapse at 3 years was 0.36. For patients who received ≤ 20% or > 20% BM blasts, the cumulative incidence of relapse at 3 years was 0.29 and 0.75, respectively (P = .0009). Four of 5 patients who underwent transplantation for ALL relapsed, including 2 patients whose disease recurred after a previous allogeneic HCT and 2 of 3 patients who underwent transplantation during a refractory relapse. Thirteen of 38 (34%) patients who underwent transplantation for a myeloid malignancy (AML, MDS, or myeloproliferative disease (MPD)) relapsed. Three of 18 (17%) patients transplanted for MDS/MPD recurred at 5.4, 5.6, and 6.7 months post-HCT. Ten of 20 patients who underwent transplantation for AML (1 in CR3 and 19 in active disease) relapsed at a median of 3.7 months (range, 2.6-22.0 months) post-HCT.

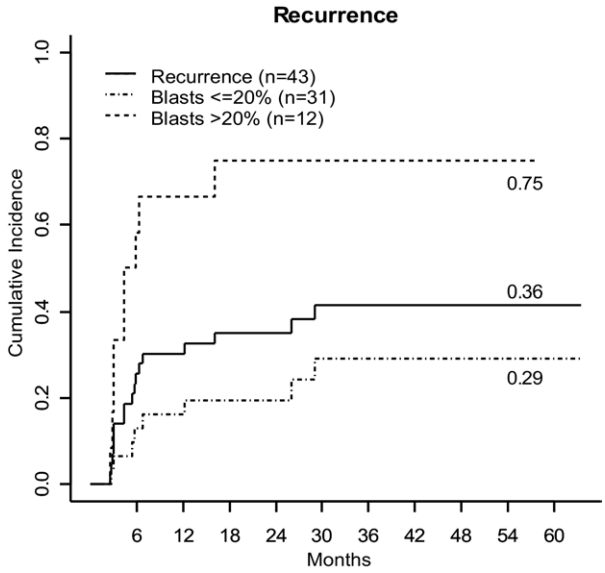

Figure 1. Cumulative incidence of recurrence.

OS and DFS

The 3-year probability of OS and DFS for the entire cohort was 0.37 (95% confidence interval [CI] = 0.24-0.57) and 0.33 ± 0.08 (95% CI = 0.21-0.51), respectively (Figure 2A). The estimated 3-year DFS was 0.39 in patients who received ≤ 20% (n = 31) and 0.17 in those who received > 20% (n = 12) blasts (Figure 2B), respectively (P = .09). Among the patients who underwent transplantation for a myeloid malignancy, the 3-year DFS was 0.61 for patients with MDS (≤ 20%) or a myeloproliferative disorder and 0.13 in the 20 patients with AML, 95% of whom had active disease at the time of HCT (P = .01) (Figure 3).

At a median follow-up of 44 months (range, 18.1-67.9 months), 17 patients were alive without disease, 14 in CR. Three patients relapsed and were salvaged by a subsequent transplantation. One relapse occurred in a child with MDS (RAEB, monosomy 7) who rejected an unrelated BMT and engrafted after a T-cell–depleted HLA-mismatched maternal PBSCT. He relapsed 7 months after the latter transplant and was alive without disease 46+ months after his third HCT, a second T cell depleted, HLA-mismatched

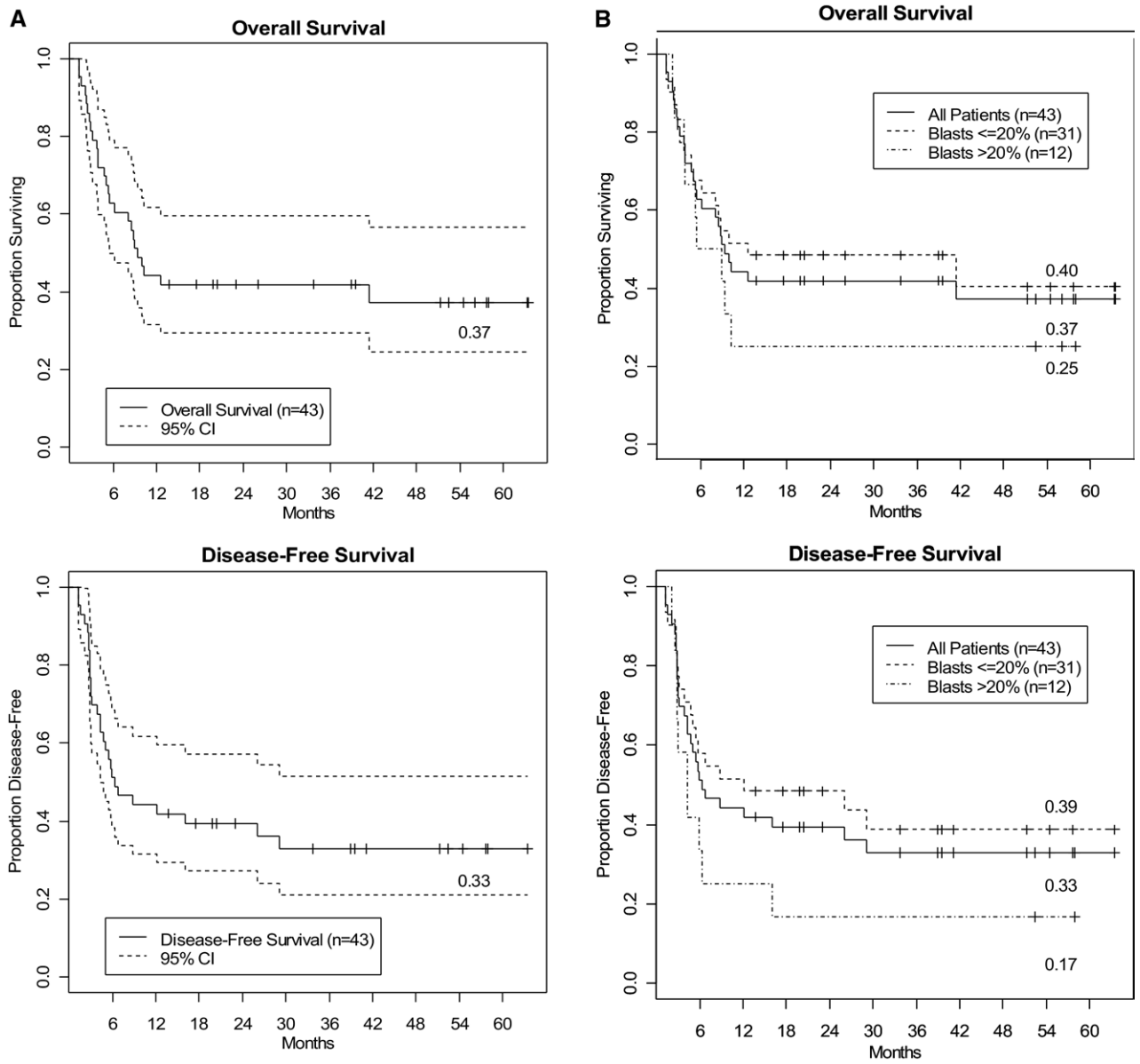

Figure 2. (A) OS and DFS (n = 43). (B) OS and DFS by blast count ≤ 20% or > 20%.

maternal PBSCT. The second patient is a 49-year-old male who underwent transplantation for AML in first refractory relapse (52% blasts), who relapsed 16 months after an HLA-matched sibling HCT and was alive without disease 43+ months after a nonmyeloablative transplant from his original donor. The third patient is a 50-year-old male who underwent transplantation for AML in first refractory relapse (20% bone marrow blasts) who relapsed 22 months post-HCT. He was alive in CR 6+ months after a second unmodified HCT from his primary donor. The only patient treated for ALL who survived disease-free is an adult who underwent transplantation for natural killer cell positive ALL in refractory first relapse (59% blasts) who was alive and well 58.0+ months after an unrelated PBSCT. All surviving patients had a Karnofsky or Lansky score of ≥ 80.

Cause of Death

Twenty-six patients died, at a median of 4.9 months (range, 1.7-41.5 months) post-HCT. The primary causes of death (Table 2) were relapse (n = 14), GVHD (n = 5), toxicity (n = 4), infection (n = 2), and graft failure (n = 1). Fatal toxicity took the form of VOD (n = 1), transfusion-related acute lung injury (n = 1), and idiopathic pneumonitis (n = 2). Fatal infectious complications included CMV pneumonitis (n = 1) and polymicrobial sepsis associated with septic shock and multiorgan failure

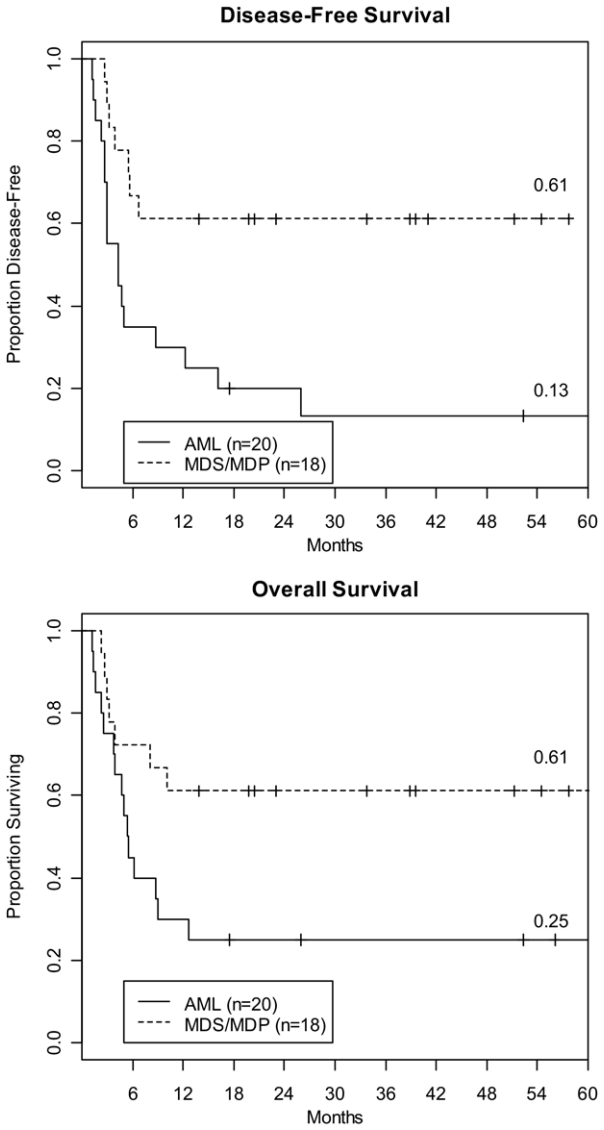

Figure 3. OS (upper) and DFS (lower) in the 38 patients with a myeloid malignancy.

(n = 1). Nonrelapse mortality for the 43 patients was 0.28 (Figure 4).

DISCUSSION

The aim of this pilot trial was to assess the antileukemic potential of cytoreduction with intravenous busulfan and melphalan, followed by unmodified allogeneic HCT in patients with an advanced or high-risk hematologic malignancy. We also sought to determine the incidence of transplant-related morbidity and mortality associated with this regimen, as well as the efficacy of tacrolimus and methotrexate for preventing GVHD. Despite the extremely high-risk nature of this patient population, as of the time of this report, 17 of 43 patients were alive and free of disease, with 14 in CR. Patients with an advanced or high-risk myeloid malignancy (median age, 49.5 years) achieved an estimated 42% OS and 35% DFS at 3 years with a relapse rate of 34%. Of the 5 patients with an advanced or refractory lymphoid malignancy, 3 of whom underwent transplantation while in refractory first or second relapse and 2 of whom relapsed after a previous allogeneic HCT, only 1 survived in CR. Although patients with lymphoid malignancies composed a small subset of the total number of patients who underwent transplantation in this trial, these results are similar to those of larger studies reported in the literature [36,37].

Despite the inclusion of heavily pretreated patients, the nonrelapse mortality at was 0 at 30 days, 16% at 100 days, and 28% at 365 days, and the incidence of VOD was < 5%. VOD was observed in 2 patients who received gemtuzumab before transplantation [38]. A similarly low incidence of VOD has been observed in allogeneic transplant recipients given other regimens that include intravenous busulfan [26,39]. However, several modifications to the protocol were needed to reduce regimen-related toxicity. Folinic acid rescue was added after each dose of methotrexate to decrease the severity of mucositis. Tacrolimus was titrated to achieve levels of 5 to 10 ng/mL, to reduce renal toxicity, and ATG was included in the pretransplantation conditioning regimen to prevent graft failure after an unrelated HCT. Despite these changes, the incidence of grade II-IV acute GVHD and chronic GVHD was low in our series. Although the relative contribution of pretransplantation ATG and posttransplantation methotrexate and tacrolimus cannot be ascertained, the observed incidences of acute (24%) and extensive chronic GVHD (7%) are consistent with those in reports demonstrating the superiority of tacrolimus and short-course

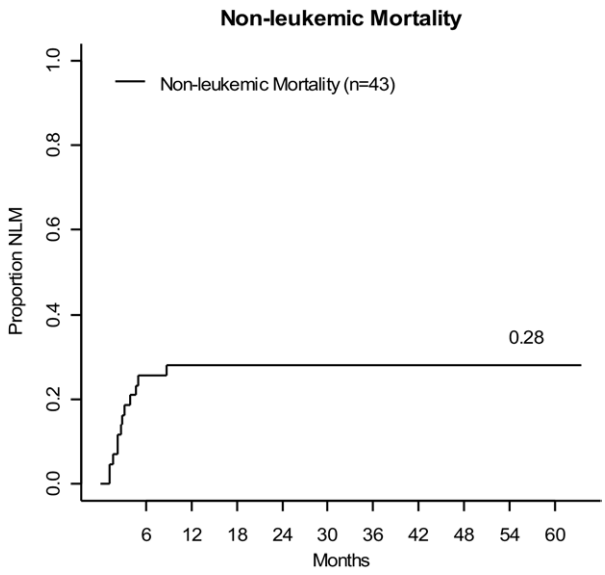

Figure 4. Nonleukemic mortality.

methotrexate in preventing severe acute and extensive chronic GVHD compared with cyclosporine A and methotrexate [27,28]. These data also support previous studies demonstrating that folinic acid rescue in methotrexate-containing regimens is not associated with an increased risk of GVHD [40,41].

The fact that each of the 40 evaluable patients achieved remission after cytoreduction with busulfan and melphalan and that 14 of the 41 patients who engrafted are alive and disease-free attests to the antileukemic activity of this regimen even in patients with refractory disease. As other studies have noted, the percentage of BM blasts at the time of HCT was an important predictor of DFS [13,15,18,36-38,42]. Clearly, interventions are needed to further improve DFS in these high-risk patients. Although nonmyeloablative (NMA) or reduced-intensity cytoreductive (RIC) regimens have been associated with a lower nonrelapse mortality, most series have not shown an improved DFS in patients with advanced hematologic malignancies [43]. A retrospective study by the European Group for Blood and Marrow Transplantation [44] comparing outcomes of patients over age 50 years with advanced AML (> CR2) given reduced-intensity or myeloablative therapy followed by an HLA-matched sibling transplant demonstrated no significant difference in 2-year estimated DFS between the 2 groups (23 ± 5 for RIC vs 21 ± 4 for myeloablative). Although cytoreduction with a RIC regimen consisting of once-daily intravenous busulfan and fludarabine followed by unmodified HCT was associated with a 1-year estimated DFS of 75% in patients who underwent transplantation for AML or MDS in CR and 34% in those with active disease [39]. In 31 patients given a NMA conditioning regimen for treatment of an advanced myeloid leukemia (> CR1) or advanced MDS, Alyea et al. [45] reported an estimated 2-year OS of 28%, compared with 16% for patients who received myeloablative therapy (P = .08). Patients with chemotherapy-resistant or rapidly growing leukemias likely will derive less benefit from NMA or RIC, due in part to the inability of these regimens to induce significant disease control before generation of a functional graft-versus-leukemia (GVL) effect. Scott et al. [46] compared transplant outcome after myeloablative therapy with targeted Bu/Cy (n = 112) versus NMA cytoreduction (200 cGy TBI, with [n = 36] or without [n = 2] fludarabine) in patients over age 40 with MDS or AML with trilineage dysplasia. Eligibility criterion for NMA in this study was < 10% blasts at the time of HCT. Despite the fact that the patients receiving a myeloablative conditioning regimen had more advanced disease before transplantation (as measured by peak International Prognostic Scoring System risk score), there was no statistical difference in progression-free survival at 3 years between the 2 cohorts (44% vs 27%) and, surprisingly, no difference in NRM (32% for myeloablative vs 39% for NMA). Although clinically extensive chronic GVHD occurred in 62% of HCT recipients who received myeloablative conditioning and in 55% of those who received NMA conditioning, disease progression remained the primary cause of death in both groups [46].

Although further intensification of pretransplantation cytoreduction has been used in an attempt to improve DFS in patients with poor-risk disease, it has generally resulted in an increase in nonrelapse mortality, negating any beneficial effect on disease control [19-21]. In contrast, prophylactic immunotherapy with donor lymphocytes [47], donor-derived natural killer cells in Kir ligand–mismatched patients [48], and/or cytotoxic T cells directed against antigens differentially expressed on leukemic cells (eg, WT1 [49,50] or PR-1 [51]) might permit establishment of an effective GVL effect early after transplantation without increasing the risk of GVHD or the need for extended immunosuppressive therapy. The median time to relapse in this study (9.8 months) and the high rate of remission induction support the use of this cytoreductive regimen as a platform on which to test adoptive immunotherapy strategies. In addition, for patients with less advanced myeloid malignancies who cannot tolerate TBI and/or cyclophosphamide due to young age, previous radiotherapy, cardiac dysfunction, or hemorrhagic cystitis, this regimen offers an alternative that merits further exploration.

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